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# Progression of carotid-artery disease in type 2 diabetic patients: a cohort prospective study

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**Abstract:** In order to assess the progression of carotid-artery disease in type 2 diabetic cohort (n=207 patients), the dynamic change in carotid intima-media thickness (CIMT) and the occurrence of plaques were followed for a period of  $31.35 \pm 10.59$  months. The mean CIMT at the beginning of the study was  $0.9178 \pm 0.1447$  mm, with a maximal value of  $1.1210 \pm 0.2366$  mm. The maximal value of CIMT changed by 0.07 mm/year. Progression of CIMT was noted in 86.8% and its regression in 7.8% of patients. The occurrence of carotid plaques was detected in 41.8% of patients. Multiple regression analysis revealed the maximal value of CIMT to be associated with diastolic blood pressure, despite mean CIMT being predicted by body mass index. The presence of peripheral arterial disease and hypo-high-density lipoproteinemia were found to be predictors for the occurrence of carotid plaques. Our data have clinical implications in predicting risk factors for the progression of carotid-artery disease in type 2 diabetic patients for their appropriate management.

**Keywords:** carotid IMT, type 2 diabetes, progression of atherosclerosis, risk factors

## Introduction

Diabetes has been defined as an independent factor for the presence of high-grade carotid-artery stenosis in the general population.<sup>1</sup> Type 2 diabetes (T2D) poses a substantial risk factor for the progression of atherosclerosis, measured by rise in carotid intima-media thickness (CIMT), expressed in length unit per patient in 1 year, and compared with the occurrence of plaques on the internal carotid artery in 1–2 years.<sup>2,3</sup>

There is a clear correlation among arterial hypertension, hypercholesterolemia, and inflammatory markers (c-reactive protein and serum amyloid concentration) as predictors of carotid atherosclerosis in patients with diabetes.<sup>4,5</sup> We determined the dynamics of progression of carotid-artery disease (CAD) in patients with T2D and determined factors that influence it.

## Patients and methods

In this prospective study, a cohort of T2D patients (n=207) were followed for a period of  $31.35 \pm 10.59$  months for dynamic changes in CIMT and the occurrence of plaques. T2D was defined based on the criteria of the International Diabetes Federation.

CIMT was measured by B-mode ultrasound using a linear transducer (7.5–10 MHz) and was performed by a single sonographer. CIMT is presented as a mean value of two measurements from both sides of the common carotid arteries. CIMT is defined as the distance from the leading edge of the first echogenic line to the leading edge

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of the second echogenic line on the scans, with the first line representing the lumen–intima interface and the second line representing the collagen-containing upper layer of the adventitia. Plaque was defined as a localized thickening lesion ( $\geq 1.1$  mm). Carotid stenosis greater than 60% was considered significant. In each longitudinal projection, the site with the greatest thickness (including plaques) was detected along the vessel from the common carotid artery to the internal carotid artery. Peripheral arterial disease (PAD) was defined as ankle-brachial index (ABI)  $< 0.9$  or  $> 1.3$ . The observer was blinded to patient risk factors.

Standard laboratory analyses were performed in all patients. Multivariate analysis was performed in order to assess the predictors for CIMT progression. The model was adjusted for age. The study was conducted in accordance with the Helsinki declaration. This study which was a part of project: Diabetic polyvascular disease, was approved by the scientific committee of Medical Faculty Skopje. At this timepoint there was no need for approval from an ethics committee. Informed consent was obtained from all patients.

## Results

In the study population, a mean value of IMT = 0.9178 mm and maximal value of CIMT = 1.1210 mm, respectively, were obtained. The maximal value of CIMT changed by 0.07 mm annually (Table 1).

Progression of carotid atherosclerosis was noted in 86.8%, followed by a change in CIMT. In 17.8% of patients, the occurrence of carotid stenosis was evident, while in 41.8% of patients, the development of new carotid plaques was noted.

Multiple linear regression analysis was performed when continuous variables from Table 2 were put into this model. The change in CIMT showed that its maximal value was predicted by the diastolic pressure value and the change in mean value of CIMT by body mass index (BMI). Predictors for the change in CIMT values annually are shown in Table 3.

Multiple regression analysis demonstrated low high-density lipoprotein (HDL) and the presence of PAD to be independent factors for the progression of atherosclerotic plaques (Table 4). In addition, ABI values, presence of carotid

**Table 1** Values of CIMT in the study population

	Minimum	Maximum value	Mean value	Standard deviation
IMT	0.60	1.1210	0.9178	0.1447
$\Delta$ IMT <sub>max</sub> /year	-0.10	0.60	0.0627	0.0732
$\Delta$ IMT <sub>mean</sub> /year	-0.50	0.57	0.0259	0.0802

**Abbreviations:** CIMT, carotid intima-media thickness; IMT, intima-media thickness;  $\Delta$ IMT<sub>max</sub>, change in maximal value of IMT;  $\Delta$ IMT<sub>mean</sub>, change in mean value of IMT.

**Table 2** Continuous variables in the study population

Variables	Mean value	Standard deviation
Systolic pressure (mmHg)	143.9	19.6
Diastolic pressure (mmHg)	86.1	9.2
Weight (kg)	82.9	13.4
Height (cm)	169.4	7.5
Waist	96.9	8.0
BMI (kg/m <sup>2</sup> )	28.7	4.0
Glycemia (mmol/L)	8.5	2.4
Total cholesterol (mmol/L)	5.4	1.4
HDL cholesterol (mmol/L)	1.0	0.4
Non-HDL cholesterol (mmol/L)	4.3	1.4
LDL cholesterol (mmol/L)	3.3	0.9
Triglycerides (mmol/L)	2.0	1.0

**Abbreviations:** BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

plaques at the beginning of the study, and the presence of intermittent claudication were also found to be independent factors.

Since postprandial glycemia was included in the multiple linear regression analysis in the progression of CAD, the same value was shown as a substantive value compared to degree of carotid stenosis. Raised amounts of glycated hemoglobin ( $HbA_{1c}$ )  $> 7\%$  were in linear correlation with maximal change in CIMT (Figure 1).

In order to analyze the operator's influence on carotid measurements, a homogeneity test of regression was used

**Table 3** Predictors of CIMT

Model	B	SD	$\beta$	t	Significance
<b><math>\Delta</math>IMT<sub>mean</sub></b>					
Constant	0.765	0.150		5.096	0.000
Plaques	1.080	0.097	0.845	11.100	0.000
Physical inactivity	9.487 <sup>-2</sup>	0.030	0.244	3.183	0.003
BMI	1.047 <sup>-2</sup>	0.004	0.220	2.885	0.006
<b><math>\Delta</math>IMT<sub>max</sub></b>					
Constant	-0.584	0.371		-1.575	0.123
Diastolic pressure	9.054 <sup>-3</sup>	0.004	0.309	2.078	0.044
<b><math>\Delta</math>IMT<sub>mean</sub>/year</b>					
Constant	-0.121	0.057		-2.127	0.040
Carotid stenosis, %	0.294	0.074	0.506	3.972	0.000
<HDL	-7.807 <sup>-2</sup>	0.027	-349	-2.876	0.007
CVD	6.526 <sup>-2</sup>	0.026	0.300	2.480	0.018
Retinopathy	-8.835 <sup>-2</sup>	0.043	-0.263	-2.072	0.045
<b><math>\Delta</math>IMT<sub>max</sub>/year</b>					
Constant	-0.487	0.121		-4.031	0.000
BMI	2.035 <sup>-2</sup>	0.004	0.898	4.592	0.000
Obesity	-0.146	0.038	-0.791	-3.832	0.000
PAD	-0.106	0.036	-0.400	-2.925	0.006
Claudication	6.924 <sup>-2</sup>	0.025	0.353	2.797	0.008

**Abbreviations:** CIMT, carotid intima-media thickness;  $\Delta$ IMT<sub>max</sub>, change in maximal value of IMT;  $\Delta$ IMT<sub>mean</sub>, change in mean value of IMT; BMI, body mass index; HDL, high-density lipoprotein; CVD, cerebrovascular disease (history of); PAD, peripheral arterial disease; SD, standard deviation.

**Table 4** Predictors for plaque progression

	B	SE	Wald	df	Significance	Exp(B)	95% CI Exp(B)	
							Lower	Upper
Plaque progression								
PAD	1.435	0.470	9.321	1	0.002	1.238	1.095	1.598
<HDL	−0.770	0.342	5.085	1	0.024	1.463	1.237	1.904
Plaque	0.950	0.407	5.457	1	0.019	2.586	1.165	5.741
Plaques, bilateral	2.380	0.445	28.621	1	0.000	10.802	4.517	25.830
Constant	−1.997	0.482	17.152	1	0.000	0.136		

**Abbreviations:** SE, standard error; CI, confidence interval; df, degrees of freedom; PAD, peripheral arterial disease; HDL, high-density lipoprotein.

when the mean and maximal values of IMT were included. It was clear that there was minimal influence of the operator on measurements ( $F=17.061$ ,  $P=0.018$ ).

## Discussion

The progression rate of CAD in high-risk populations has been previously reported to be 15%–20% annually.<sup>6–8</sup> Our results are comparable with previous studies – ARIC (Atherosclerosis Risk in Communities Cohort) and IRAS (Insulin Resistance Atherosclerosis Study) – with regard to progression of CIMT of 0.1 mm annually in the T2D population.<sup>6–8</sup>

Randomized controlled studies have shown an inverse correlation between HDL cholesterol and CIMT value and its progression in the population with high cardiovascular risk and those with T2D.<sup>9</sup> IMT, which comprises the intima and media, is susceptible to the influence of risk factors for artery disease. The enlargement of the intima is a result of the atherosclerotic process, and media enlargement is a response to vascular remodeling in high-artery-pressure conditions.<sup>10</sup> The SANDS study<sup>11</sup> demonstrated that the arterial pressure and low-density lipoprotein (LDL) cholesterol are defined as independent factors with the greatest risk for progression of CAD. Our results show logistic regression dependency

in plaque progression; respectively, they showed linear regression dependency on change in IMT mean ( $\Delta\text{IMT}_{\text{mean}}$ ) from hypo-HDL-emia. Total cholesterol is an independent predictor for the occurrence of carotid plaques according to our results. Lipid fractions, LDL cholesterol, and triglycerides are important factors in the progression of carotid atherosclerosis in the general population and in those with diabetes.<sup>11</sup> However, lipid fractions were not shown as independent factors in the progression of carotid atherosclerosis in the Rotterdam study.<sup>12</sup> This is most likely due to the high atherogenicity of LDL cholesterol and non-HDL cholesterol, even when they are within their normal range. Accomplishing lower LDL and non-HDL values is important in decreasing the progression of CAD in T2D.

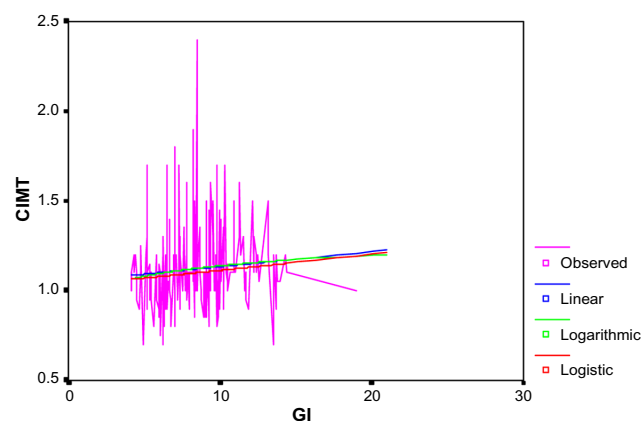
Arterial hypertension is a predictor for CIMT value. In a meta-analysis, it was clear that for every decrease of 5 mmHg in arterial pressure, regression of IMT of 0.01 mm/year resulted.<sup>13</sup>

Age, male sex, smoking, and BMI are the best independent factors in carotid-atherosclerosis progression.<sup>14,15</sup> Accordingly, our data demonstrate that BMI is a predictor for progression of IMT values ( $\Delta\text{IMT}_{\text{mean}}$  and  $\Delta\text{IMT}_{\text{max}}$ ) annually. The long prediabetic phase and late diagnosis of diabetes are independent factors in the progression of CIMT;<sup>16</sup> however, in our study this was not evident.

PAD occurrence and ABI value have been shown as predictors in CAD progression, which is demonstrated in our results. The relationship of ABI with CAD defines not only PAD but the presence of diabetic polyvascular disease.<sup>17</sup>

We also examined the influence of glycemic control on the progression of carotid stenosis. The obtained glycemia values and IMT were in log-linear correlation. The degree of carotid stenosis was correlated with the glycemic value.

The correlation of vascular disease in diabetic patients with glycemic control measured by HbA<sub>1c</sub> was shown in Selvin et al's meta-analysis.<sup>18</sup> Postprandial glycemia has been shown to be a powerful predictor against HbA<sub>1c</sub> compared to the correlation with diabetic vascular disease.<sup>19</sup> In the



**Figure 1** Relationship of glycemia to CIMT.

**Abbreviations:** CIMT, carotid intima-media thickness; GI, glycemia.

DECODE study, postprandial glycemia is an independent predictor for CAD and mortality in patients with T2D.<sup>20</sup> Our results demonstrate the correlation of carotid atherosclerosis with fasting glycemia.

In our study, bias might have been present because of the selected values of CIMT through which the progression of atherosclerosis is defined. For this reason, a multiple linear regression analysis for continuous variables of CIMT was used.

Progression of the carotid plaque due to multivariate regression analysis is predicted with the former presence of plaques, low HDL cholesterol and presence of PAD, ABI value, age, systolic blood pressure, and total cholesterol. Change in CIMT value is predicted with diastolic blood pressure and BMI according to linear regression analysis.

These results are also meaningful when making comparative analysis of certain risk factors in the progression of vascular disease in certain localizations in T2D. Hyperglycemia is a crucial factor in the development of PAD in diabetes, and arterial hypertension and low HDL cholesterol for the development of CAD in diabetes. This spectrum of significance on certain risk factors was supported with our results.

## Conclusion

Our results indicate that the dynamics of CIMT<sub>max</sub> were determined with diastolic blood pressure, despite CIMT<sub>mean</sub> being predicted by BMI. Presence of PAD and hypo-HDL-emia were found to be predictors for the occurrence of carotid plaques. These results have clinical implications in finding the risk factors for the progression of CAD in T2D patients for appropriate clinical management.

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## Disclosure

The authors report no conflicts of interest in this work.

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